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Total Synthesis of Brevetoxin B. 1. CDEFG Framework

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With its imposing structure, brevetoxin B (**1**), produced by *Gymnodinium breve* Davis, stood as a formidable challenge to synthetic chemists since its discovery and structural elucidation in 1981.[1] Brevetoxin's beautifully arranged molecular assembly includes 11 *trans*-fused rings, each containing an oxygen atom, with each fusion consisting of a C−C bond separating two adjacent ring oxygens and with all adjacent substituents flanking the oxygens placed *syn* to each other except on ring K. Its unprecedented architecture, its association with the "red tide" catastrophes,[2] and its potent neurotoxicity and interference with the function of sodium channels attracted serious attention from chemists[3] and biologists[4] alike. We now wish to announce, in this and the following communication,[5] the total synthesis of brevetoxin B (**1**) in its naturally occurring form.

Figure 1 outlines the strategic bond disconnections and retrosynthetic analysis of **1**. The adopted strategy benefited from convergency (oxocene disconnections) and synthetic technologies developed in these laboratories specifically for constructing oxocene[6] and tetrahydropyran[7] systems.

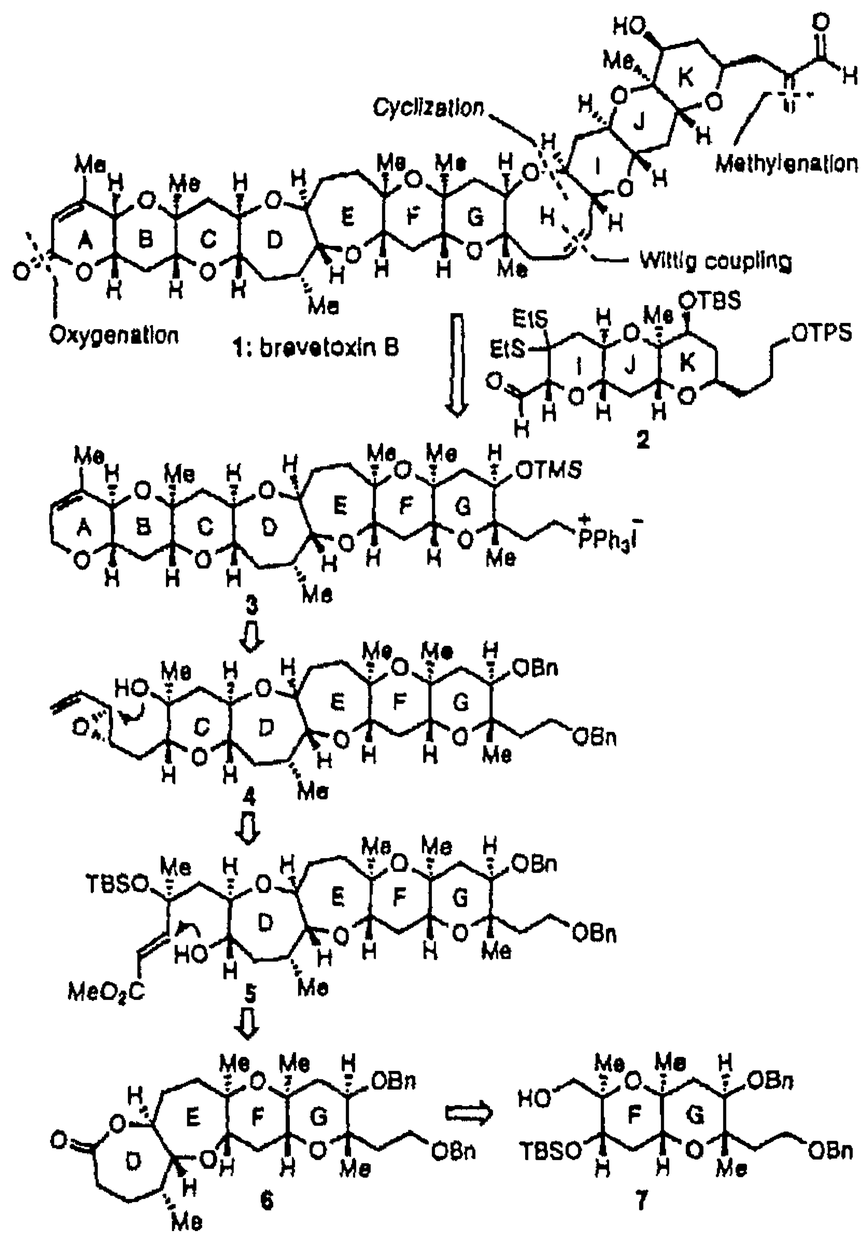

Figure 1. Strategic bond disconnections and retrosynthetic analysis of brevetoxin B (**1**).

The construction of the CDEFG framework **4** described herein began with the previously reported intermediate **7** (Scheme 1).[8] Swern oxidation of **7** followed by a Wittig reaction with the appropriate reagent furnished, in 99% overall yield, compound **9** via aldehyde **8**. Hydrogenation of **9** and selective, acid-induced monodesilylation gave alcohol **11** via **10** in 97% overall yield. Oxidation of **11** in a sequential fashion using Swern and $NaClO_2$ conditions resulted in carboxylic acid **12** (97%), which upon desilylation with TBAF led to **13** (91%). Lactonization of hydroxy acid **13** by the Yamaguchi method[9] and enol triflate formation gave **15** via **14** in 84% overall yield. Generation of the higher order cuprate derived from the lithio derivative of iodide **17a**[10] and **17b** followed by coupling[11] with triflate **15** and partial acid-induced orthoester hydrolysis resulted in formation of **18** via **16** (84% yield over two steps, *ca.* 2.4:1 ratio at C* in favor of the desired isomer, *vide infra*). Regio- and stereoselective hydroboration of **18** followed by oxidative workup and alkaline hydrolysis furnished hydroxy acid **19** in 73% overall yield. Finally, lactonization[9] of **19** and separation of the C* epimers afforded pure lactone **6** (60% yield, plus 25% of its C* methyl epimer), whose structure was determined by X-ray crystallographic analysis (see ORTEP drawing of a derivative[10] of **6**, Figure 2).

The fusion of the remaining three rings onto the DEFG system **6** to afford the targeted polycyclic framework **4** proceeded as depicted in Scheme 2. Thus, conversion of lactone **6** to its enol triflate (97%) followed by Cr/Ni-mediated coupling[12] with

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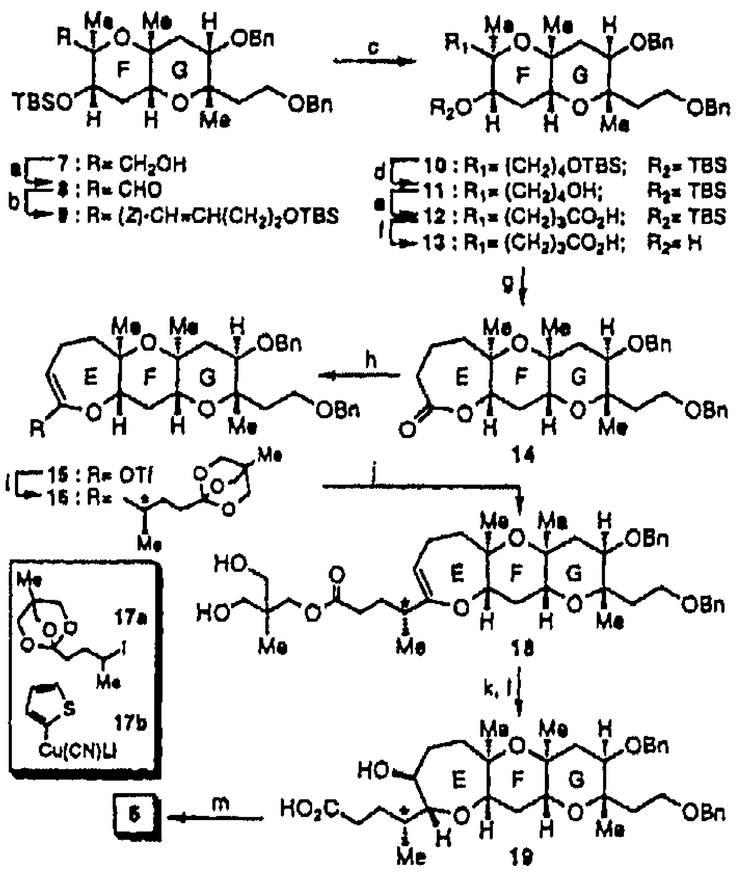
Scheme 1. Construction of DEFG Ring System **6**[a]



[a] Reagents and conditions: (a) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 7.0 equiv of Et_3N, 0.5 h, 100%; (b) 2.0 equiv of $TBSO(CH_2)_3PPh_3^+I^-$, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then **8**, 0.5 h, 99%; (c) H_2, 0.1 equiv of Pd/C (10%), 0.1 equiv of Na_2CO_3, EtOAc, 25 °C, 12 h, 100%; (d) 1.0 equiv of CSA, CH_2Cl_2/MeOH (1:1), 0 °C 1 h, 97%; (e) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 7.0 equiv of Et_3N, 0.5 h; 1.5 equiv of $NaClO_2$, 2.0 equiv of NaH_2PO_4, 2.0 equiv of 2-methyl-2-butene, *t*-BuOH/H_2O (2:1), 25 °C, 1 h, 97%; (f) 5.0 equiv of TBAF, THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 90%; (h) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, −78 °C, 2 h, then 1.5 equiv of Tf_2NPh, −78 → 25 °C, 93%; (i) 6.0 equiv of **17a**, 10.0 equiv of *t*-BuLi, Et_2O, −120 → −78 °C, 0.5 h, then 5.0 equiv of **17b**, −78 → 30 °C, 0.5 h, Et_2O/THF/HMPA (1:1:1), then **15**, −78 → 0 °C, 2 h, 84%; (j) 0.3 equiv of PPTS, DME/H_2O (1:1), 25 °C, 100%; (k) 6.0 equiv of BH_3·THF, 0 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H_2O_2, 89%; (l) 2.0 equiv of LiOH, DME/H_2O (1:1), 25 °C, 82%; (m) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et_3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 60% of **6**, plus 25% of its C* epimer (after column chromatography).

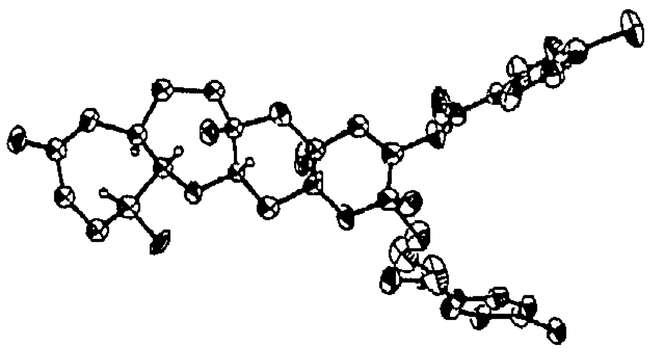


Figure 2. ORTEP of the bis(*p*-bromobenzoyl) derivative of **6**.

aldehyde **20**[10] furnished alcohol **21** (66%, mixture of epimers), which was deoxygenated via xanthate **22** (89%) by the Barton method[13] to afford **23** (67%). Regio- and stereospecific hydration of **23** via hydroboration/oxidation gave alcohol **24** (82%), which was silylated, leading to **25** (96%). A series of reactions involving DIBAL-H-mediated ester cleavage (98%), Dess−Martin oxidation (85%), Horner−Emmons olefination (99%), and acid-induced selective desilylation (100%) afforded α,β-unsaturated ester **5** via **26**, **27** and **28**. Exposure of **5** to KH led to the formation of the CDEFG ring system **29** in 90% yield via a stereoselective Michael-type reaction.[14] Extension of the ester side chain via DIBAL-H reduction and phosphorane condensation furnished, via aldehyde **30** (97%), the α,β-unsaturated ester **31** (98%), which was reduced to allylic alcohol **32** (96%). Sharpless asymmetric epoxidation[15] of **32** using (+)-DET as the chiral auxiliary gave the corresponding hydroxy epoxide (99% yield), which was further oxidized to the aldehyde and subjected to a Wittig reaction to afford terminal olefin **33** (80% over two steps), and thence hydroxy epoxide **4** upon TBAF-induced desilylation (100%).

The elaboration of **4** to the ABCDEFG framework **3**, the coupling of the latter to the IJK system **2** and the completion of the total synthesis of brevetoxin B (**1**) are described in the following communication.[5,16]

Acknowledgment. See following communication.[5]

Supplementary Material Available: See following communication.[5]

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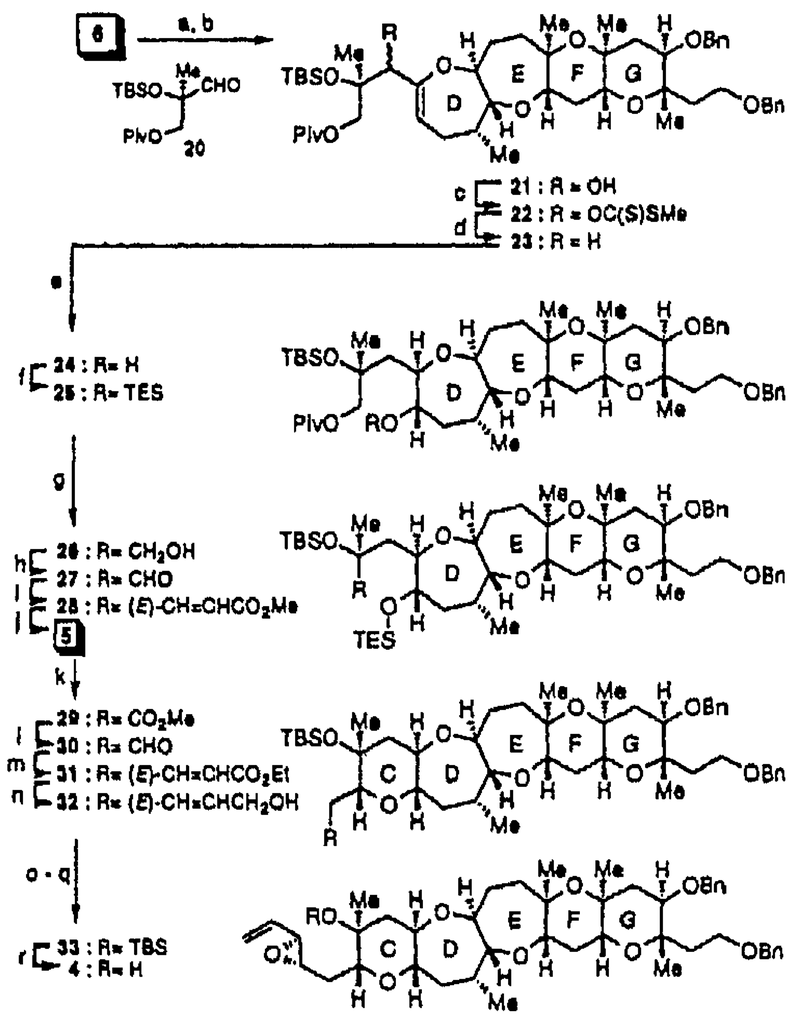
Scheme 2. Construction of CDEFG Ring System **4**[a]



[a] Reagents and conditions: (a) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, −78 °C, 2 h, then 1.5 equiv of Tf_2NPh, −78 → 25 °C, 97%; (b) 6.0 equiv of **20**, 6.0 equiv of $CrCl_2$, 0.02 equiv of $NiCl_2$, DMF, 25 °C, ultrasound, 3 h, 66%; (c) 3.0 equiv of CS_2, 50.0 equiv of KH (added over 5 h), Et_2O, then 10.0 equiv of MeI, 25 °C, 89%; (d) 4.0 equiv of n-Bu_3SnH, 0.1 equiv of AIBN, benzene, 80 °C, 67%; (e) 5.0 equiv of BH_3·THF, −30 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H_2O_2, 82%; (f) 2.0 equiv of TESOTf, 2.5 equiv of 2,6-lutidine, CH_2Cl_2, −70 °C, 1 h, 96%; (g) 2.5 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 5 min, 98%; (h) 1.7 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 2 h, 85%; (i) 2.0 equiv of KHMDS, 0.2 equiv of 18-crown-6, 5.0 equiv of $(MeO)_2P(O)CH_2CO_2Me$, THF, 0 °C, 0.5 h then add **27**, 3 h, 99%; (j) 1.0 equiv of CSA, CH_2Cl_2/MeOH (2:1), 25 °C, 1 h, 100%; (k) 2.0 equiv of KH, THF, 25 °C, 2 h, 90%; (l) 1.3 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 2 min, then 3.0 equiv of MeOH, 97%; (m) 2.0 equiv of Ph_3PCHCO_2Et, CH_2Cl_2, 25 °C, 12 h, 98%; (n) 2.5 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 96%; (o) 0.2 equiv of $Ti(O^iPr)_4$, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of *t*-BuOOH (5 N in decane), CH_2Cl_2, −20 °C, 5 h, 99%; (p) 5.0 equiv of SO_3·pyridine, 10 equiv of Et_3N, CH_2Cl_2/DMSO (4:1), 0 °C; (q) 1.2 equiv of NaHMDS, 1.5 equiv of $CH_3PPh_3^+Br^-$, THF, 25 °C, 1 h, 80% (over two steps); (r) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 100%.

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